REMARKS

Applicant respectfully requests reconsideration. Claims 26-48 were previously pending in this application. Claims 37 and 48 were amended to depend from claims 36 and 47, respectively. Claims 26 and 38 have been amended to recite the limitation "cell-mediated" immunity. Support for this amendment can be found in the instant specification at least on page 1, line 17. As a result, claims 26-48 are pending for examination with claims 26 and 38 being independent claims. No new matter has been added.

Rejections under 35 U.S.C. §112

Claims 26-48 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter.

The Examiner states that the term "not antisense" as recited in the claims is not supported in the specification as filed. The instant specification describes oligonucleotide analogs having "both therapeutic efficacy (through antisense or other means) and immunopotentiating activity." (page 8, lines 6-7). Applicant directs the Examiner to MPEP 2173.05(i) which reads:

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion."

As the specification gives a number of alternatives for the activity of phosphorothioate oligonucleotide analogs, including immunopotentiating activity and antisense, the specification as filed therefore provides literal support for the term "not antisense.

Therefore, withdrawal of the new matter rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 26-48 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking in written description.

The Examiner further states that claims 26-48 specify a genus that does not have written support in the instant specification. The Examiner states that "the specification must provide sufficient distinguishing identifying characteristics of the genus" such as "structure, physical or chemical properties, functional characteristics, and structure/function correlation." The Examiner states that not all oligonucleotides elicit an immune response, and cites McIntyre et al. (Antisense Research and development 3: 309-322, 1993) in support of this.

The Examiner states that "it was art known that not all phosphorothioate oligonucleotides analogs elicit an immune response." However, the Examiner has not presented evidence to support that this was known or widely accepted in the art at the time the instant application was filed. The Examiner cites McIntyre et al. (Antisense Research and Development 3:309-322, 1993) as concluding that "some phosphorothioate oligonucleotides do not elicit non-specific effects or immune responses." Applicant respectfully disagrees with this broad interpretation of the teachings of McIntyre. While McIntyre et al. states that "reports have begun to emerge regarding the usefulness of antisense phosphorothioate oligonucleotides in vivo in diverse models", McIntyre goes on to say that "relatively little is known about the in vivo side effects of these oligonucleotides on different tissues." (McIntyre, p317-318) McIntyre et al. teaches only one oligonucleotide, the p65 sense oligonucleotide, for which the data were interpreted as indicating a sequence-specific immune effect. The McIntyre reference cites two other papers (Branda and Mojcik) as saying that their sense oligos have similar sequence-specific effects. However, McIntyre notes that these have no sequence homology with the p65-sense oligo. McIntyre goes on to state that "it is possible that the p65-sense oligonucleotides bind to some unidentified mRNA that includes a natural antisense RNA to p65, thus acting as a synthetic antisense sequence." (p318).

The Examiner cites Wu et al. (Anesthesiology 94: 1119-1132, 2001 esp. page 1129, right column, first paragraph, last sentence), as teaching that "phosphorothioates molecules may interact non-specifically with cellular targets, resulting in extensive cellular cytotoxicity". However, Wu et al. support the use of phosphorothioate oligonucleotides for the purpose of sequence-independent immune stimulation, stating that "sequence-independent effects, including immune stimulation...may be caused by the polyanionic character of the phosphorothioate oligonucleotides" (Wu et al., page 1129, right column, first paragraph, second sentence.)

Therefore, the teachings of Wu et al. do not support the broad conclusion that the "response due to the administration of a phosphorothioate oligonucleotide analog is sequence dependent."

The instant specification describes oligonucleotide analogs with at least one phosphorothioate bond in the backbone. It was found by the inventors that these phosphorothioate oligonucleotides can induce stimulation of a cell-mediated or humoral immune response in a sequence non-specific manner. However, in the interest of furthering the prosecution of the instant application, Applicant has amended claims 26 and 38 to limit the immune response to a cell-mediated response (also termed "local" immune response in the specification, see for example page 1 line 17). The teachings of McIntyre et al. are directed to a humoral immune response and therefore these teachings are not applicable to claims directed to a cell-mediated immune response.

Accordingly, withdrawal of the rejection of claims 26-48 under 35 U.S.C. §112 is respectfully requested.

Claims 26-48 were rejected under 35 U.S.C. §112 as allegedly lacking enablement. The Examiner acknowledges that the specification is "enabling for a method of stimulating a local immune response in a human by administering one phosphorothioate oligonucleotide analog, ISIS 2105" but alleges that it "does not reasonably provide enablement for a method of stimulating a humoral immune response in a human using any phosphorothioate oligonucleotide analogs in a patient with any type of cancer, any type of infection, and in combination with any type of surgery."

The nature of the invention is summarized in the current office action, page 8. The instant claims are drawn to administering by a route selected from the group consisting of inhalation, opthamalic, intranasal, parenteral, oral and intradermal to the human as an immunopotentiator an amount of a phosphorothioate oligonucleotide analog effective to stimulate an immune response, wherein the phosphorothioate oligonucleotide analog is not antisense. The immune response may be an antibody response. The response may be humoral or systemic.

It has been established in the art that induction of an immune response is beneficial in the treatment of various disorders such as infectious disease and cancer. At the time of filing,

methods for identifying human subjects having cancer or an infection were routine. Anti-infective and anti-cancer agents were also known, and surgical procedures were similarly routine.

One unexpected finding of the present invention is that oligonucleotides having at least one phosphorothioate linkage in their backbone can stimulate immune responses in a sequence independent manner. A common element of all the pending claims is the recitation of a phosphorothioate oligonucleotide analog that functions as an immunopotentiator. As defined in the specification, a phosphorothioate oligonucleotide analog is an oligonucleotide having at least one of its phosphodiester bonds replaced with a phosphorothioate linkage. The immunopotentiating effect is independent of the sequences of the oligonucleotide analogs used herein.

However, in the interest of furthering prosecution, Applicant has amended the claims to limit the immune response to a cell-mediated immune response.

The Examiner relies on his interpretation of Allison et al. (Molecular Immunology 28: 279-284, 1991) and Iversen et al. (Anti-Cancer Drug Design 6:531-538, 1991) to support his conclusion that the state of the art was unpredictable at the time of filing. The Examiner cites Allison et al. as stating that "the efficacy of a stimulator of an immune response such as an adjuvant is judged by determining the types and levels of antibodies produced when an antigen is administered with the adjuvant" (Allison et al., page 279, right column, first complete paragraph). Applicant points out that Allison states that traditionally this is the way an immune response had been evaluated. Evaluation of antibody type and levels is only one way of measuring an immune response. One way a humoral immune response may be evaluated is by measuring antibody production. Conversely, one way a cell-mediated immune response may be evaluated is by measuring production of inflammatory cytokines such as. IL-2, IFNγ, and TNFβ. Applicant has demonstrated efficacy of the phosphorothioate oligonucleotide analogs in both antibody production and cytokine production. As stated above, in the interest of furthering prosecution Applicant has limited the claims to cell-mediated immune response. The efficacy of the phosphorothioate oligonucleotide analog in eliciting both a humoral and cell-mediated immune response has been demonstrated in the Examples.

The Examiner cites Mojcik et al. (Clinical Immunology and Immunopathy 67(2): 130-136, 1998), Branda et al. (Biochemical Pharmacology 45(10):2037-2043, 1993), and McIntyre et al. as teaching that "induction of splenomegaly and stimulation of B-lymphocyte proliferation in mice injected with phosphorothioate oligos occurs unpredictably in a manner that is dependent on the nucleotide sequence of the phosphorothioate oligonucleotide analogs." As stated above, the Examiner has not presented evidence to support his broad conclusion that this was known or widely accepted in the art at the time the instant application was filed. Each of these references represents a very small number of examples and the effects may be explained by antisense activity.

The Examiner further cites Liang et al. (J. Clin. Invest 98(5): 1110-1129, 1996) as teaching that although "certain oligodeoxynucleotides can stimulate murine B cells, much less information is available on the immunostimulatory capacity of these materials for human B cells" and that "it is not possible to extrapolate results obtained from mouse to man". However, the instant specification provides examples that demonstrate the ability of the phosphorothioate oligonucleotide analogs to induce an immune response in mice (Example 8), rats (Example 7) as well as humans (Examples 9 – 11).

The Examiner cites Vollmer et al. (Antisense and Nucleic Acid Drug Development 12:165-175, 2002) for the teaching that "non-CpG T-rich ODNs are always less efficient and potent than CpG ODNs", and that the mechanism of action by non-CpG "remains to be elucidated". Applicant points out that the results of Vollmer et al. are dosage-specific and that there is an optimal dose for activity of T-rich nucleic acid which may not be reflected in the data of Vollmer et al. In support thereof, the Examiner is directed to Figure 1 of Vollmer et al. which shows immunostimulation by a T-rich nucleic acid that is 17 nucleotides in length (ODN 5192). The dose-response data for this nucleic acid demonstrate that its stimulatory capacity increases substantially with increasing dose. The data highlighted by the Examiner in Figure 2 of Vollmer et al. corresponds to a single dose and there is no indication that it is necessarily the optimal dose for the nucleic acids tested. Additionally, the fact that phosphorothioate nucleotide analogs may be less immunostimulatory than CpG ODNs under some conditions is not relevant to patentability. Applicant need only show that the claimed method achieves its intended result, not that it achieves a better result than prior art methods. Applicant has met this burden by

demonstrating that phosphorothioate nucleotide analogs are immunostimulatory. Finally, understanding mechanism is not a prerequisite to patentability.

The Examiner cites McCluskie et al. (Vaccine 19:2657-2660, 2001) for the teaching that "a polythymidine nucleic acid twenty nucleotides in length...did not have an immunostimulatory effect in immunized mice" and Jones et al. (Vaccine 17:3065-3071, 1999) for teaching "a T-rich immunostimulatory nucleic acid lacing CpG dinucleotides as a negative control for testing ODNs in vivo". Again, the data of McCluskie et al. and Jones et al. correspond to a single dose of nucleic acid. Presumably, it is a dose at which the tested CpG nucleic acids were active. However, as argued herein, that dose may not be optimal for a non-CpG nucleic acid such as the phosphorothioate nucleotide analogs of the instant invention. Vollmer et al., McCluskie et al. and Jones et al. therefore stand for the proposition that higher doses of non-CpG nucleic acids may be necessary for immune stimulation (as compared to CpG nucleic acids). They do not support the proposition that phosphorothioate nucleotide analogs are not immunostimulatory.

The specification must be enabling as of the filing date (MPEP 2164.05). The evaluation of whether the instant specification would have been enabling at the time of filing—in the case of this continuation application, the priority date of March 25, 1994requires consideration of the level of skill in the art and the state of the art at that time. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). The teachings of McCluskie et al., Jones et al., Vollmer et al., and Mojcik et al. would not have been known in the art at the time of filing and are therefore should not be considered in the evaluation of enablement or unpredictability of the instant claims.

The structure of nucleic acids was known in the art at the time of the invention, as was the structure of a phosphorothioate linkage within a phosphodiester backbone. Moreover, it was routine in the art to make such phosphorothioate linkage containing oligonucleotides. At the time of filing, methods of making and using nucleotide modifications such as altered sugar moieties, inter-sugar linkages and base units were known in the art. The specification further teaches how to test phosphorothioate oligonucleotide analogs for immunostimulatory activity. The specification teaches how such an immunopotentiator can be identified and provides various

assays that could be used for this purpose. The specification gives examples of the use of phosphorothioate oligonucleotide analogs to induce an immune response in mice, rats, and humans.

Accordingly, the claimed invention is enabled in its scope with respect to the recited methods of treatment, in view of the teachings of the specification and the knowledge in the art at the time of filing, and withdrawal of this rejection is respectfully requested.

Double Patenting Rejection

The Examiner rejected claims 26, 28, 29, and 30 as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 6,727,230 (Hutcherson et al.) in view of U.S. Patent 5,456,882 (Walker et al.).

Applicants may consider filing a Terminal Disclaimer if some claims are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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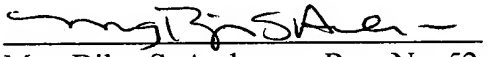
By: 

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Docket No.: C1037.70049US00
Date: July 25, 2006
x07/27/06x